THE CLINICAL SIGNIFICANCE OF ABNORMAL BLOOD-PRESSURES

By SIR HUMPHRY ROLLESTON, BART., K.C.B., M.D., Hon. D.Sc., D.C.L., LL.D.

Regius Professor of Physic in the University of Cambridge, England.

REPRINTED FROM INTERNATIONAL CLINICS, VOL. III, SERIES 38

THE CLINICAL SIGNIFICANCE OF ABNORMAL BLOOD-PRESSURES

By SIR HUMPHRY ROLLESTON, BART., K.C.B., M.D., Hon. D.Sc., D.C.L., LL.D.

Regius Professor of Physic in the University of Cambridge, England.

The history of blood pressure really begins with Stephen Hales (1677–1761), minister of Teddington, who with a sound training of newtonian physics applied this knowledge to biology and physiology. Before 1723, he tied tubes into the arteries and veins of animals and estimated the pressure in the capillaries, thus being far in advance of his time. In a mare he found that the blood pressure was equal to a column of blood of eight to nine feet. Nearly a century passed before the subject was further investigated, and then Poiseuille (1828) employed a U-shaped mercurial manometer (hæmodynometer), which, as van Leersum points out, was but a step from the mercurial column which Hales used to estimate the pressure of the sap in a pruned vine. To this in 1847, Carl Ludwig added a float with a pen to record the variations of the blood pressure on a revolving cylinder (kymograph). Experimental methods of estimating the arterial blood pressure were then pursued by a number of observers, such as A. Fick (1864, 1885), with a spring manometer, Marey's sphygmoscope (1875), modified by Hürthle into a rubber manometer, and von Frey's metal tonograph.

In the meanwhile Bright (1836) had noticed the hard pulse in renal disease as judged by the finger, and has therefore been called "the first student of the hypertensive problem" (Janeway, 1913). The clinical estimation of blood pressure by instrumental means was first attempted by Vierordt in 1855 by measuring the weight necessary to stop the arterial pulsation; but von Basch in 1876 invented a sphygmomanometer on this principle which was applied locally over an artery and was widely used. Marey compressed the whole of the forearm, later confining this method to the finger. Mosso

and Hürthle introduced modifications. Ryle has recently recalled pious attention to F. A. Mahomed's laborious observations on blood pressure made between 1874 and 1881, not with a sphygmomanometer but with his own form of Marey's sphygmograph, which led him to anticipate much that is now known and far more easily verified. The present sphygmomanometric methods became generally available as a result of Riva-Rocci's modification of von Basch's instrument with a piece of rubber tubing to surround the arm in 1897, and by Hill and Barnard's independent description of a somewhat similar instrument about the same time. In 1901, von Recklinghausen showed that as a result of the insufficient width of these rubber tube armlets a higher systolic pressure was registered than actually existed; this was confirmed by C. J. Martin and remedied in his Mummery's, and other modifications of the Riva-Rocci model. In 1901, Harvey Cushing saw the Riva-Rocci instrument in use in the medical wards of the Ospitale de S. Matteo, Pavia, and, with full acknowledgments, published an account of "Routine Determinations of Arterial Tension in Operating Room and Clinic" in 1903, having previously stimulated Drs. H. W. Cook and Erlanger to construct the instruments known by their names. In 1902, Vaschide and Lahy gave an exhaustive review of the subject up to date. G. W. Crile in 1903 published his experimental and clinical research entitled "Blood Pressure in Surgery"; in the following year, however, a Committee on Surgical Research of the Harvard Medical School issued a report with the conclusion that "the adoption of blood-pressure observations in surgical patients does not at present appear to be necessary as a routine measure." The publication of Korotkoff's auscultatory method in 1905 has made estimation of the diastolic pressure both easy and accurate for all conditions except some cases of aortic regurgitation.

THE LIMITS OF THE NORMAL

Variations in blood pressure, like those of the pulse rate, are both physiological and pathological, and it may be difficult to draw a hard and fast line between what Sir James Goodhart (1845–1916) called "normal abnormalities" on the one hand and the earliest signs of disease on the other. Our conception of the normal is derived from the average; and the enormous statistics of American

Insurance Companies, such as those of Fisher (19,339 candidates), Symonds (150,419), and of students and school children, such as those of Alvarez (8,934 female, 6,000 male freshmen), Stocks, and Dawson, have provided a basis for a standard scheme of blood pressures in health at different ages in the two sexes. Disease has been variously defined; it has been regarded as a departure from the condition usual for the healthy individual, but, be it noted, this is very different from saying it is a departure from the average condition of a large number of people. In individuals there are considerable differences in the level at which the blood pressure is set; thus among male students Alvarez found 45 per cent. with a systolic pressure above 130, and 22 per cent. above 140 mm. Hg, while among the female students the corresponding percentages were 12 and 2. Low blood pressure without any obvious cause (essential hypotension) is not so frequent; among 10,142 males, obtained by combining the figures of Alvarez and Barach there were 279 or 3.55 per cent. (Fossier). Healthy and otherwise normal persons may have a blood pressure lower or higher than the average as a result of their hereditary constitution or make up, and such departures from the average in young people, when not excessive and unassociated with symptoms, should not cause anxiety. Very high pressures in the young should suggest contracted white kidneys, but the moderate degrees of variation may be devoid of serious import. It is of course very different when in older persons a moderate hyperpiesis steadily increases.

The constitutional factor, after the eclipse due to the advent and intervention of bacteriology, has now again come under serious consideration as an important element in disposing to disease, in other words attention is being paid to the "soil" as well as to the "seed." Both high and low blood pressures appear to be familial traits, and have been regarded as associated with special constitutions; the physical characters of a low blood pressure subject being the hyposthenic habit, with a long narrow chest, liability to be easily affected by cold, slack and easily tired, and of a high blood pressure person the hypersthenic, broad shouldered and broad-chested, athletic, vigorous, and of the John Bull type (Hurst: Ryle). The people with constitutional or essential low blood pressure have the advantage of longevity, and there is not any tendency for their pressure to

become progressively lower, whereas in families with their blood pressures set moderately high there is liability for it, in unfavorable circumstances, to become permanently higher, so that they may, but do not necessarily, provide a succession of deaths from gradual cardiac failure, uræmia, cerebral hemorrhage, and angina pectoris; for this reason much more attention has been paid to high than to low blood pressure.

Weiss from an extensive study of family trees showing the results of hypernormal pressures concluded that high blood pressure was a constitutional disease and that it was a dominant Mendelian characteristic. This therefore suggests a much more pessimistic outlook for those with a blood pressure set on the high side as compared with those whose habitual low pressure commonly promises length of days, and it might be suggested that the term "diathesis," defined by Jonathan Hutchinson as any bodily condition of prolonged peculiarity of health giving proclivity to definite forms of disease, or more briefly a persisting morbid proclivity, would be more applicable to the subjects of a hereditary raised blood pressure, than "constitution." The hypertensive diathesis has been insisted on by O'Hare, Walker, and Vickers, by Alvarez (1924), and others. On the other hand it might be urged, and this is more than a mere verbal juggling as it bears on the prognosis, that these individuals with a high blood pressure are disposed to react to strain, mental or dietetic, in such a way as to develop a decidedly morbid blood pressure, and thus to come more within George Draper's definition of constitution as "the aggregate of hereditary characters influenced more or less by environment, which determines the individual's reaction, successful or unsuccessful, to the stress of environment" than to be a diathesis which, as just defined, is a persisting morbid proclivity. Draper, who conducts a Constitutional Clinic on anthropometric lines at the Presbyterian Hospital, New York, has tabulated the constitutional characters of the subjects of high blood pressure and chronic nephritis; they differ considerably in the two sexes: the males are small with shorter heads than in other disease groups, whereas the females are very large, heavy faced, resembling the type liable to gall-bladder disease rather than that of those subject to peptic ulcer, with longer heads than in other disease groups, masculine, and showing physical signs on the lines of acromegaly and previous

pituitary activity; they are more prone than others when pregnant to show high blood pressure and nephritis. Both sexes have the short necks popularly associated with a liability to apoplexy. As the result of an investigation into the blood pressure of women as influenced by the sexual organs, Alvarez and Zimmermann found that masculine and sexually abnormal women have a higher blood pressure than normal women, and conclude that essential hypertension or Allbutt's hyperpiesia (namely without renal disease) is a bodily peculiarity inherited equally by boys and girls, but ordinarily suppressed in women by the ovarian or other secretions, and when the pelvic organs are subnormal the disease may appear in women as early as in men. This view may be correlated with the liability of women with high blood pressure to be less fertile than ordinary women, and also with the high blood pressure of the menopause, particularly in the obese.

Enough has perhaps been said to emphasize the variations of blood pressure that may occur in individuals, comparable to that between races in tropical and temperate regions, and to show that these variations may be inborn or constitutional and not acquired or due to disease induced by environment or infection, and that it may be of about the same significance as an habitually quicker or slower pulse than that of most people. The phrase "blood pressure", meaning thereby an unduly raised pressure, is a popular cry, now somewhat usurping the place formerly taken by gout as a respectable complaint, and panic on insufficient grounds is not an infrequent result. It is no doubt wise to recognize that those with a hereditary blood pressure set above the average should take more care in avoiding overeating than the hypotensives, but this advice should be given with tact, for worry is of course a potent excitant of raised blood pressure.

Consideration of the clinical significance of abnormal blood pressure should begin with a reference to the distinction between temporary and permanent elevations. A single estimation may of course, from nervous apprehension, give an unduly high systolic reading, and any deduction from this may therefore be erroneous; but apart from this well known fallacy a transient and quite considerable rise of blood pressure may occur in bouts of toxæmia, even in children (Allbutt). Such temporary rises are suitably described

by the word hyperpies*is* which Allbutt employed as synonymous with high blood pressure and in contrast to hyperpies*ia,* defined in his posthumous work as a disease independent of the kidney disease with its own characters, the chief being high systolic and diastolic blood pressures.

Raised blood pressure is merely a sign which may be due to many causes, some organic, permanent and prone to be progressive, others transient and functional. It seems therefore highly probable, as Fortescue Fox's clinical experience suggests, that in people about fifty years of age hypertension may be a passing affection curable by hygienic measures, being an episode due to nervous disturbance of the strain of life in men and of the menopause in women. Moschcowitz (1928) describes as pseudo or transient arteriosclerosis the tightening up of the arteries, due to muscular hyertrophy, in acute glomerulo-nephritis, which disappears with recovery. Pines' observations appear to show that such periods of raised pressure may leave behind them arteriosclerotic changes in the retina without obvious arteriosclerosis elsewhere, the retinal change being due to the poison responsible for the high blood pressure, as is stated by G. Evans (1923) when describing diffuse hyperplastic sclerosis.

Here, perhaps, may be mentioned the subject of *"the silent gap"* or "trou auscultatoire" which has attracted little attention in this country, though considerably discussed in France and in America by Sewell. Everyone must have been puzzled by occasionally finding that, contrary to the rule, the systolic blood pressure as estimated by the finger was higher than by the auditory method. White and Mudd in America and Gibson in this country have recently summarized the history of this auscultatory gap. Noted in 1917 by Cook and Taussig, it was investigated in France by Gallavardin, Tixier, Lian, and others, and found to occur more often in the second phase of the auditory curve, namely below that marking the maximum systolic pressure, and above the loud third phase; it is most frequent in cases of high blood pressure; Norris, Bazett and McMillan, however, state that it is more frequent in the fourth phase; and much more often in repeated than in the first observation, and add that venous engorgement may play a part in its production. Its practical importance is that it may give rise to mistakes in estimating the real height of the systolic pressure, for this may be

missed if the mercury is pumped up from below, and the end of the loud third zone may be taken as representing the maximum systolic pressure. To be certain of avoiding this under-estimation, the manometer should always be pumped up at once to 250 mm. Hg and then allowed to run down, so as not to miss the first zone of the systolic pressure above a possible silent gap.

Difference in the systolic pressure in the two arms may be physiological, meaning thereby nothing more than evidence of an anatomical abnormality in the vessels; its reputed occurrence in pulmonary tuberculosis (vide p. 96) is of very doubtful significance. It occurs in some cases of aneurysm of the aorta and its large branches, corresponding to the inequality of the pulses, and is more often due to atheromatous patches at the orifice of the subclavian than to pressure on the trunk of the subclavian by an aneurysm. The pressure of a cervical rib on the subclavian naturally produces a small pulse and lower blood pressure in the vessels of the corresponding arm. As a result of trauma, either unilateral or bilateral and differing in degree, the blood pressures in the two arms have been found to be nearly always different (E. F. Cyriax).

A higher systolic pressure in the lower limbs than in the arms is normal in the erect position, but in the horizontal position in healthy young persons the pressures in the limbs should be equal. In aortic incompetence, arteriosclerosis, Graves' disease, exophthalmic goitre the systolic pressure is higher in the legs than in the arms when the patient is lying flat, so that it is not pathognomonic of any one condition. But a much higher blood pressure in the arms than in the lower limbs is characteristic of co-arctation of the aorta.

HYPERTENSION

In the routine examination of a patient a knowledge of the blood pressure, like that of the state of the tongue, pulse rate and temperature, clears the ground, and when abnormal directs attention in certain directions. Thus after eliminating temporary elevation due to nervousness and deciding that the systolic pressure is too high to be regarded as solely a constitutional variation, the question arises whether it is renal or "essential"; if examination of the urine and renal functional tests, such as estimation of the blood urea, are negative it may be hyperpiesia. In idiopathic high pressure the

diastolic is not raised to the same degree as the systolic pressure, but still the pulse or differential pressure is seldom so large as in arteriosclerosis. The higher systolic pressures—over 200 mm. Hg—are in favor of renal change, though it may be thought difficult, even in the absence of evidence of renal insufficiency, to exclude a renal origin for raised pressure. The next step is to try to determine whether or not the high pressure is associated with arteriosclerosis, and to search for any cause in the environment, such as worry or overfeeding, or in the body, such as focal sepsis, which can have an etiological relationship. If these enquiries draw blank, what course should be adopted? Is it advisable to reduce the blood pressure or to be content with efforts to prevent further rise by directions as to a healthy manner of life and removal of adverse factors. The details of treatment do not come within the scope of this address, but it may not be out of place to quote the aphorism of the late Dr. W. H. Dickinson in reference to the commonly combined disease, chronic nephritis, that "the great danger of the disease is that some one will find it out and try to treat it" as a warning against overtreatment of the symptom of high blood pressure by starvation and excessive depletion of the patient. A high blood pressure can be reduced more easily than an unduly low one can be raised; but often the individual is thereby made to feel worse, and this has led to the belief that the raised blood pressure is a compensatory adjustment and is set for the individual at what is the most suitable level. Since the time of Cohnheim's dictum that raised blood pressure is a physiological reaction to increase the pressure in the remaining glomeruli of a damaged kidney, it has often been argued that a raised pressure is useful in maintaining an efficient circulation in parts of the body—kidney, myocardium, brain, or some other capillary areas—where otherwise there are difficulties; to reduce the pressure, therefore, would appear to be merely to treat a symptom; further it may be urged that a spontaneous fall of blood pressure precedes the onset of œdema.

MacWilliam pointed out that the existence of the hypothetical compensatory function of raised blood pressure might be investigated by artificially lowering the blood pressure by vaso-dilators, in order to determine if any functional disturbance—renal, cardiac, or respiratory—resulted. Accordingly Reid took up the question of renal

efficiency, but in this respect failed to find any support for the widely accepted view that the raised pressure is a compensatory factor. Clifford Allbutt (1925) held up the compensatory hypothesis to scorn and in advising treatment of it *per se* spoke highly of the beneficial effects of diathermy. It may well be that, though the rationale of diathermy in reducing blood pressure is unknown, it may correct or neutralize the effects of some metabolic vice and so remove or arrest the cause of raised blood pressure. It is, however, important to have further information about the state of patients whose blood-pressure is in the first instance lowered by diathermy.

What of the future of people with a persistently raised blood pressure? Statistics in the mass show that their mortality is much higher than the average, but it is unsafe to apply this general verdict to the individual, for there are so many examples of prolonged life with a markedly raised pressure, and also of temporary periods of raised pressure. How will death come? From statistics in private practice among the well-to-do in New York, Janeway (1913) found that in order of frequency the modes of exitus were gradual cardiac failure, uræmia, apoplexy. Which of the three, the heart, the kidneys, or the brain will be mainly responsible, or in other words what part of the circulatory system will succumb first, must depend on factors such as (1) the inborn strength or weakness of the myocardium, the kidneys, or the blood-vessels, (2) on the presence of acquired disease, for example in cases of primary nephritis, the death obviously is likely to be renal in nature; thus in ten cases of young subjects (under thirty-four) with chronic glomerulo-nephritis, seven proved fatal from nephritic results (six uræmia and one from heart failure), and three from intercurrent infections (Branch and Linder); and (3) the co-existence of arteriosclerosis, especially of the cerebral vessels; thus Andrewes' figures of the incidence of cerebral hemorrhage at St. Bartholomew's Hospital showed that though the apparent maximum is in the sixth decade, correction for the age distribution of the population proved that the liability of the individual to this mode of death increases steadily up to old age. The occurrence of cerebral hemorrhages depends more on the state of the cerebral arteries than on the actual height of the systolic pressure. Norris indeed states that less than 15 per cent. of patients with a

systolic pressure of 200 mm. Hg or more die from cerebral hemorrhage, which certainly occurs in patients whose blood pressure has never been known to be above 170 mm.

Norris has sorted out two groups of high blood pressure: (1) the systolic and the diastolic (120–150) are both high with a special liability to uræmia and cerebral hemorrhage, and (2) a high systolic pressure with a moderate increase in the diastolic pressure, in which death from cardiac failure is the probable ending. In cases with high systolic and relatively low diastolic pressure there is generalized arteriosclerosis, and Fishberg says that these form a definite group characterized by advanced age, infrequency of complaint of symptoms directly due to high blood pressure, aortic sclerosis, and finely granular kidneys.

A point of some interest, which requires further elucidation at the hands of general practitioners, is the time that it takes for a serious degree of high blood pressure to develop; sometimes it is undoubtedly a slow process extending over fifteen or twenty years, but in other instances it is rapid. Keith, Wagener and Kernohan of the Mayo Clinic describe a malignant form of high blood pressure, usually in the fourth decade, running a rapid course with characteristic retinal changes, and diffuse general hypertrophy of the arterioles of the obliterating nature.

HYPOTENSION

What is the *significance of a habitually low blood pressure* without an obvious cause, such as Addison's disease, amyloid disease, malignant or other cachexias? A low systolic pressure may be found in about 3 per cent. of people otherwise normal and often with a history of familial longevity. Just as it is difficult to draw a hard and fast line between what may be regarded as within the normal variations and a definitely high systolic pressure, so is it far from easy to say where definite or essential hypotension begins; 110 mm. Hg systolic pressure given by Norris, Fossier, McCrae and others as the dividing line, would appear to be rather too high, and probably a systolic pressure below 100 (Janeway, 1904), and a diastolic of 60 mm. Hg would be more correct. That a comparatively low blood pressure is compatible with perfect health and activity is cer-

tain; McWilliam says that some athletes in good training have systolic and diastolic pressures of 105 and 65. This subject of the blood pressure of healthy athletes is of considerable interest and can be well studied at universities. The late R. W. Michell (1860–1916), who had much experience among rowing men at Cambridge, found that their systolic pressures were: "When just awakened and lying in bed; 95–100 mm. Hg; after rising, and while moving about the room it is 100–115; two hours after hard exercise, and immediately on lying down 130–125; from this highest point the fall becomes rapid, so that after the man has been lying down for ten minutes it is often 106–110." The pressure on waking is described, on the analogy of basal metabolism, as the basal blood pressure by Addis, who from observations on American recruits found the basal systolic and diastolic blood pressures 99 and 71 as compared with daytime estimations of 127 and 78. Dr. C. H. S. Taylor, who has succeeded to Michell's practice, has given me the following memorandum which tends to shake the impression that healthy athletes may be expected to show a low blood pressure: "After an experience of nine years amongst undergraduates I have not found the majority of athletes to have a low blood pressure. I find no consistent picture for either the systolic or diastolic pressures, and am inclined to regard any but a gross divergence from the recognized normal as a personal idiosyncrasy without significance."

Though a moderately low blood pressure, like a moderately high one, may be found in perfectly healthy persons, especially in early adult life and as a hereditary or constitutional trait, a decidedly lower pressure is found in association with a group of signs and symptoms pointing to want of stamina and vigor, undue fatigability, tendency to faint, giddiness, palpitation on moderate exertion, sensitiveness to cold, as shown by acrocyanosis, and what Mackenzie called x-disease and subsequently ascribed to intestinal stasis (vide Lane). In some persons a drop of 50 per cent. in the systolic pressure and a corresponding fall in the diastolic pressure with a tendency to syncope follows standing up. Orthostatic or cyclic albuminuria in overgrown, lanky boys is another and so to speak localized manifestation, and should not excite foreboding as it is a disease cured, not caused, by time. No one cause explains all cases of low blood pressure. A low blood pressure forms part of the status lymphati-

cus; in this connection it is interesting to recall Symmers' view that anaphylactic death may occur in status lymphaticus as the result of sensitization of the body by a specific nucleoprotein formed as the result of necrosis of the cells in the germinal follicles of the lymphatic glands. Friedlander cautiously put forward the hypothesis that capillary stasis due to histamine poisoning is responsible for essential hypotension. Lastly as a cause of what may appear to be idiopathic or essential low pressure, often about 100 mm. Hg, tobacco smoking must be mentioned.

IN CARDIAC DISEASE

As the normal blood pressure is chiefly maintained by the heart and the peripheral resistance, failure of either of these two factors should logically be followed by a fall of blood pressure; this certainly occurs in anaphylactic and histamine shock and acute conditions of heart failure, especially in coronary thrombosis in which a sudden fall of the systolic pressure may reach 80 mm. Hg with a diminution in the differential pressure and the clinical aspect may be that of shock. But in chronic cardiac failure this does not hold good; in cardiac failure secondary to high blood pressure the readings show a raised pressure either as persistent evidence of the cause or in addition on account of the compensatory factor which comes into play in other forms of cardiac insufficiency. Systolic and diastolic pressures may be practically normal in patients with dyspnœa, cyanosis and œdema as the result of abnormal adjustments. In 1906, H. J. Starling showed that in "heart disease ordinarily so-called" the systolic pressure is not below the normal. Some years later Cowan and Fleming stated that in mitral stenosis the systolic blood pressure is more often above than below the normal. The explanation of this compensation was provided later by Starling and Anrep's demonstration that when imperfectly supplied with blood the vasomotor centre brings about a compensatory rise in the general blood pressure, thus confirming Cushing's earlier demonstration in 1901, that the vasomotor centre exerts a regulating influence whereby anæmia of the medulla oblongata is prevented when the intracranial pressure is increased, as in cerebral compression; this the vasomotor centre does by raising the cerebral blood pressure to a slightly higher level than the intracranial pressure. Hence in cardiac failure both

the systolic and diastolic pressures may become raised (Wolferth).

As the difference between the systolic and diastolic pressures—the pulse-pressure or, better, the differential pressure—in normal conditions represents the work done by the heart muscle, a diminution of this differential pressure points to cardiac insufficiency and so is a bad prognostic. But the converse, namely that a large differential pressure is evidence of a vigorous myocardium does not necessarily follow, for it also occurs in certain morbid states, such as arteriosclerosis, exophthalmic goitre, arteriovenous aneurysm and complete heart block.

In health exertion calls forth a rise in both the systolic and diastolic pressures, but, as there is a greater rise in the systolic pressure, the differential pressure becomes larger; in cardiac debility, on the other hand, exertion produces a fall in the systolic pressure and the pulse pressure diminishes. Attempts have rightly been made to utilize the pulse or differential pressure in estimating the operative risk from the strain thereby exerted on the cardio-vascular system; Cashman employed the "pulse-pressure test in pre-operative estimation of the reserve strength of the cardio-vascular system" by observing the effect of exertion as shown by the change in the height of the systolic pressure and the size of the pulse-pressure; but Mackenzie (1918) threw cold water on it. More recently Moots has advocated the criterion of the "pressure ratio" or the percentage obtained by dividing the pulse-pressure by the diastolic pressure, thus $\frac{40 \text{ pulse-pressure}}{80 \text{ diastolic pressure}} = 50$ per cent. is the normal and most suitable for operation; if, however, the pressure ratio is high or low there is danger, thus $\frac{20 \text{ P.P.}}{80 \text{ D.P.}} = 25$ per cent. is inoperable, but if the ratio is between 30 and 70 per cent. the case is probably operable. He has also been trying another test called the "energy index": the systolic and the diastolic pressures (120 plus 80) are added together and multiplied by the pulse rate 72 and of the result (14,500) only the numerals of the thousands (14) are taken, and cases with an index of 12 to 18 are regarded as operable.

In *angina pectoris* the blood pressure was formerly assumed to be universally high, probably on account of relief obtained from vaso-dilators and Brunton's work sixty-one years ago. But it is

now clear that this is not constant; Clifford Allbutt (1915) summed the matter up by saying that in the majority of cases the blood pressure is normal. Angina, or at any rate anginoid pain, is due to several causes; it often occurs in persons with habitual high blood pressure, and apart from this the severe pain alone, just as in renal or biliary colic, may raise the blood pressure. Mackenzie (1923) discussed the relation of high blood pressure to angina in a spirit of philosophic doubt; but he pointed out that in rare instances of aortic regurgitation there is a direct relation between the height of the blood pressure and the onset of the attacks, so that conversation or taking the blood pressure brings on an attack, the pressure rising and falling as the pain becomes more intense and diminishes. He also considers that in some cases a high pressure with repeated attacks is a bad sign.

In the syndrome of thrombosis of the coronary arteries causing pathologically cardiac infarction and clinically the status anginosus which vaso-dilator drugs usually fail to relieve, there is a sudden fall of blood pressure; in a patient with anginoid pains a high blood pressure, therefore, would militate against a diagnosis of this condition.

The pulsus alternans can be detected by the sphygmomanometer, though not so satisfactorily as by a pulse tracing. Its bad prognostic significance as evidence of an overtaxed heart, and often of a degenerated cardio-vascular system, is well known. As alternating action of the heart has been observed in animals poisoned by digitalis and in rare instances in patients under its influence, the use of this drug has been thought to be dangerous; but Windle and others have shown that it can be given with benefit, at any rate for a time. The pulsus alternans is usually associated with a high blood pressure, and indeed may disappear when it falls, the prognosis being worse with a high pressure.

In *aortic regurgitation* the systolic pressure is somewhat raised and the diastolic much lowered so that the pulse-pressure, better called the differential pressure, is much increased. The well-marked difference between the systolic pressure in the arm and leg in the recumbent posture, the height being much greater in the leg, was pointed out in 1909 by Hill, Flack and Holtzmann; three years later, Hill and Rowlands supplemented the earlier paper by numer-

ous readings from cases of aortic reflex, both when uncomplicated and when combined with mitral disease, the maximum difference between the arm (142) and leg (295) pressures in these records was 153 mm. Hg. Hare confirmed these results and, by finding a pressure in the arm of 275 and in the leg of 350 mm. Hg, diagnosed aortic incompetence in the absence of the ordinary physical signs. In this connection it may be noted that, though most prominent in, and at first regarded as pathognomonic of aortic incompetence, a pressure higher in the legs than in the arms has since been found in other conditions, such as abdominal aortitis (Heitz; Gallavardin), arteriosclerosis, high blood pressure, and exophthalmic goitre. In 1914, J. R. Murray, working under MacWilliam's inspiration, carried the investigation further by finding that the systolic and diastolic pressures were often higher in the distal than the proximal segments of the two extremities, the systolic pressures in a descending scale being in the order of calf, thigh, forearm, upper arm. As I pointed out in 1912, the arm-leg difference in the systolic pressure is best marked in well compensated and uncomplicated (by mitral disease) aortic incompetence; it is much less marked in early cases, when the compensation is failing and in combined aortic and mitral disease, as indeed Hill and Rowlands' records show; that in recently established aortic incompetence, before compensation has developed, it is slight or may be absent; that the occurrence of paroxysmal tachycardia in a case of aortic reflex diminished the arm-leg difference; and that fever, like immersing the legs in hot water (Hill and Rowlands), diminishes it by lowering the systolic pressure in the legs. The arm-leg difference is thus not constant in or pathognomonic of aortic incompetence; Williamson, who found it absent in eight out of twenty-two well-marked cases, suggests that it depends on arterial thickening rather than the aortic leak.

In aortic incompetence the fifth phase of the auscultatory curve is persistent, and, if, as may happen, the distinction between its beginning and the end of the fourth phase (which determines the diastolic pressure) is indistinct, I have found it impossible to determine the diastolic pressure.

Digitalis and Blood Pressure. The effect of the intravenous injection of large doses of digitalis on blood pressure in healthy animals is well known to be pressor. The fallacy that may result

from applying physiological observations on normal animals to human patients was well illustrated in the view held, until shown to be erroneous by Sahli, Mackenzie, (1911), and his co-workers (Cushny and Price), that it was dangerous to give digitalis by the mouth in cardiac failure secondary to high blood pressure, because by constricting the peripheral vessels and so raising the arterial blood pressure further harm, such as cerebral hemorrhage, might be induced. In those days it was customary to get over the dilemma either by giving strophanthus, which pharmacologically has little vaso-constrictor effect, or by, as it was expressed, guarding the digitalis by combining it with a vaso-dilator, such as liquor trinitrini, though the effect of the vaso-dilator drug would have passed off long before that of the digitalis would begin. Personally I remember a case of a man with the failing heart of high pressure origin who had an attack of hemiplegia while under digitalis, and my feeling approaching that of guilt for malpraxis, much relieved later when this universally accepted doctrine was overthrown; so powerful was this belief that though I had failed to find a rise of blood pressure in patients taking digitalis, it seemed more probable that either the manner of its administration or my estimation of the blood pressure was at fault than that the canon of the pressor effect of digitalis was untrue for medicinal dosage.

Not only is there not any significant rise of blood pressure as the result of therapeutic doses of digitalis in man, but there may be a fall which, as Cushny pointed out, is a result of the improved cardiac action; for when the circulation is weak and the blood supply to the brain insufficient the vasomotor centre is aroused to improve the condition by contracting the peripheral vessels; as the circulation improves under digitalis, the excessive activity of the vasomotor centre disappears, and the fall in blood pressure is thus evidence of the general improvement of the circulation and the relief of cerebral anæmia. As a remedy to raise constitutional low blood pressure digitalis is disappointing.

ARTERIOSCLEROSIS

The relation of high blood pressure to arteriosclerosis, whether causal or secondary, has been much discussed, and will not be mentioned further here than to say that I follow Sir Clifford Allbutt in

believing that long-continued high pressure is not due to arteriosclerosis, but may cause it, or that both may be due to a common toxic factor. The significance of high blood pressure in a clinical case of arteriosclerosis is obviously grave, for the combination of diseased vessels and a high blood pressure must increase the liability to arterial rupture. Further the presence of high blood pressure in arteriosclerosis would, on the data provided by Bordley and Baker, appear to suggest, if not to justify, a probable diagnosis of disease of the vessels of the medulla oblongata, for among twenty-four cases of generalized arteriosclerosis these observers found fourteen with high blood pressure, all of which showed arteriolar sclerosis in the medulla oblongata and in the kidneys, whereas in the remaining ten, in which the blood pressure was normal, the arterioles in the medulla oblongata were healthy. Keith, Wagener, and Kernohan, however, did not find more marked changes in the arterioles in the medulla than elsewhere in the brain. If it is justifiable to assume that retinal arteriolar sclerosis means a similar change in the medullary arterioles, some support for Bordley and Baker's contention is supplied by O'Hare and Walker's observation that in fifty cases of peripheral arteriosclerosis with a systolic pressure under 145 mm. Hg, one case only showed definite changes in the retinal arteries, whereas in fifty cases of peripheral arteriosclerosis with a systolic pressure over 145 mm. Hg 68 per cent showed retinal arteriosclerosis. The raised blood pressure in the cases with arteriolar sclerosis in the medulla is explained by Starling and Anrep's physiological law that reduction of the amount of blood reaching the brain, presumably that part concerned with vasomotor control, calls forth a compensatory rise in the systemic arterial blood pressure. Cutler's examination of forty unselected brains, though not disproving the contention that interference with the blood supply to the vasomotor centre is the cause of high blood-pressure, showed that the interference is not due to gross vascular changes.

RENAL DISEASES

In *renal disease* a low blood pressure is found in amyloid disease; in the later stages of cases in which the systolic blood pressure has been high it may fall considerably, even in the absence of cardiac failure or other obvious cause, such as infection. In some high

blood-pressure patients a late cachectic stage occurs in which it has been thought that the symptoms are due to the accompanying fall of blood pressure (Dumas and Dubouloz); Batty Shaw has described sudden hypopietic crises of comparatively short duration accompanied by collapse, and suggests that these may be due to the formation by autolysis of histamine-like bodies in areas deprived of their blood supply by arterial obliteration; it is possible that a similar explanation, though the process is not so acute, may hold true for the cachectic fall of blood pressure. In acute nephritis there is usually a moderate rise in the blood pressure (30 mm. Hg), and apart from uræmia a high pressure, such as 200 mm. should suggest an acute attack on existing chronic nephritis; in nineteen out of Christian's fifty-five cases of primary acute nephritis, the blood pressure was not raised. In hydræmic (chronic parenchymatous) nephritis with œdema there is a moderate rise of blood pressure, usually about 160 mm. systolic. In the contracted white kidney, which may follow chronic parenchymatous nephritis or come on insidiously or remain latent until uræmic convulsions occur, the blood pressure approaches, or, in the latent cases in youth, may surpass that in chronic interstitial nephritis. In azotæmic nephritis without œdema (chronic interstitial nephritis) the systolic blood pressure is almost constantly high and may be 250 mm. or even higher.

PULMONARY DISEASES

Acute lobar pneumonia, like other acute infections, would be expected to depress the blood pressure, but there are many exceptions and disturbing factors, especially anoxæmia, to neutralize the depressor influences, which are specially seen in toxic cases, causing a fall of as much as 20 mm. Hg, which if progressive is naturally a grave omen. As the condition of the heart and the pulse rate is always a cause of anxiety, it is not perhaps surprising that attempts have been made to correlate the pulse rate and the blood pressure so as to obtain help in prognosis; twenty years ago the late G. A. Gibson formulated the attractively worded dictum that when the systolic pressure, expressed in millimetres of mercury, does not fall below the pulse rate per minute, the outlook is good, and vice versa; but its mathematical formulary has not been justified by further experience; Newburgh and Minot in America and Geoffrey Evans (1920) in

England found that the systolic pressure was higher in fatal cases than in those ending in recovery; in Evans' cases the difference was not great, but the clinical aspect of the patients with the higher systolic and diastolic pressures was worse than the others. The pulse-pressure was smaller in the fatal than in the non-fatal cases.

In *pulmonary tuberculosis* a low blood pressure is not uncommon and has been thought especially by Marfan and Potain to be somewhat characteristic of the earliest stages and in those disposed to it; its presence is not surprising in persons run down and with lowered resistance, but a definite diagnosis on these grounds alone could not be entertained. In some of these cases the adrenal glands may be tuberculous, and to their insufficiency the low pressure and other signs of Addisonism may possibly be due. In declared cases a low pressure has been regarded as an indication of liability to relapse, and there is no doubt that in febrile and particularly in toxic and advanced cases the systolic pressure may fall to 100 mm. Hg, and this has been ascribed to tuberculin which has a depressor action. But the systolic pressure may remain normal in the early stages, and that there is any characteristic feature of the blood pressure in pulmonary tuberculosis has been denied by Janeway (1915) and Shalet, and by Naucler although he found hypotension in 60 per cent. of early cases. Stivelman examined 701 tuberculous patients and found the blood pressure in the early stages within the normal limits, and, like many other observers, lower in active and advanced cases than in quiescent and fibroid cases.

It has been stated that the blood pressure may differ in the two arms, being usually lower on the affected and, when both lungs are involved, on the more severely diseased side (R. J. Cyriax); but this also has been disputed (Halls Dally), and considering the comparative frequency of a difference of 10 mm. Hg in the brachial arteries (Phipps says in 20 per cent.), which may be due to other causes (abnormalities in the vessels, arteriosclerosis, past injury), little significance can be attached to its occurrence in pulmonary tuberculosis.

ABDOMINAL DISEASES

In *gastro-intestinal conditions,* apart from those causing severe pain, such as lead and other forms of colic and gastric crises, the

blood pressure tends to be low. This has been stated to hold good particularly with visceroptosis (Fossier). Constipation, contrary to what might be expected from the pressor effect of protein derivatives, such as tyramine, appears not to exert any influence on blood pressure in man, and in women to be associated with a slightly lower mean blood pressure (Alvarez, McCalla, and Zimmermann). Allbutt (1915) definitely stated that obstinate constipation and dilated colon did not raise the blood pressure, though without giving the statistical basis and differentiation between the sexes provided by Alvarez and his co-workers. Rapid and complete thrombosis of the portal vein, like coronary thrombosis, causes a sudden fall of blood pressure and symptoms of shock due to dilatation of the veins in the splanchnic area.

The liver has so many functions that it might be anticipated that among its antitoxic or protective activities there would be the destruction or arrest of pressor bodies, such as tyramine and guanidine compounds. But this is not borne out by the observation of hepatic disease; in cirrhosis the blood pressure is certainly not high and indeed is generally low, and the same holds good in "catarrhal" (infective) jaundice and malignant disease. In spirochætosis icterohæmorrhagica the blood pressure would naturally be expected to fall as in other febrile infections, and this was found to occur by Nolf and Firket, the systolic falling to 90 and the diastolic as low as 50 mm. Hg; but Dawson, Hume, and Bedson deny this and state that in contrast to the enteric group of diseases the systolic pressure ranges about 120 mm. Hg.

In connection with this absence of any evidence of increased blood pressure in hepatic disease the effects of liver extracts in lowering experimental hypertension induced by the injection of guanidine compounds and also in some cases of essential high blood pressure in man is of interest. Major, Stoland, and Buikstra report that there is not any proof that this extract owes its depressor effect to choline, histamine, or peptone; on the other hand MacDonald and Burnett find that the extract, though free from protein and peptone, contains relatively small quantities of histamine and relatively large amounts of choline, that the depressor effect may be produced by a proper combination of these two bodies, but is more probably due to some unknown substance.

NERVOUS DISEASES

As shown by experiments (Cushing (1901), and Dixon and Halliburton), increase in the intracranial pressure above that in the cerebral vessels, thus producing anæmia of the brain, is followed by a rise in blood pressure above the extravascular pressure so as to maintain the blood supply to the medulla oblongata. In 1903, Cushing demonstrated this sequence in clinical cases of sudden cerebral compression, as by hemorrhage—meningeal and intracerebral. In slow-growing tumors and hydrocephalus there is time for accommodation to be effected so that as long as there is not any increase in the intracranial pressure the arterial pressure is not raised. Cushing pointed out that in traumatic concussion the rise of blood pressure, if it occurs, is slow, whereas in compression it is rapid. The rise of blood pressure following the onset of cerebral hemorrhage is salutary as it tends to prevent death from failure of the bulbar centres; attempts to reduce it, for example by bleeding, are therefore illogical and contra-indicated, save in the presence of cyanosis in which a small venesection, both on general grounds and because venous stasis has been found to increase the amount of cerebrospinal fluid (Tzanck and Renault) seems reasonable. Lumbar puncture on the other hand should be tried. It is stated by Dumas that if some hours or days after a cerebral hemorrhage the blood pressure is low or continues to fall the prognosis is grave, whereas a return to its level before the onset makes the outlook more cheerful. Although the rise of blood pressure is a compensatory process, a very high pressure, such as 300 mm., shows that there must be a large hemorrhage and so is ominous.

The condition of the blood pressure in acute meningitis, in which there is increased pressure of the cerebrospinal fluid, has been discussed by Robinson, Fairley and Stewart, and well summarized by Worster-Drought and Kennedy; in acute fulminating cases of cerebrospinal fever, in which there is meningococcal septicæmia, the pressure, as in other acute infections, is depressed; but in the course of meningococcal meningitis the blood pressure may be raised, and, when the symptoms are severe, reach 180-190 mm.; Robinson and Sophian considered that the blood pressure is generally raised, but according to Worster-Drought and Kennedy and Fairley

and Stewart the average blood pressure taken continuously throughout the course of the disease is below 120 mm.; they, however, found the mortality higher among the cases with a pressure above 120 mm. than in the cases below that level. It would appear probable that the pressure of the cerebrospinal fluid around the medulla oblongata is only raised above that in the arteries of the part at certain times, and that only then does the vasomotor centre take up its compensatory function of raising the general blood pressure.

True neurasthenia is associated with a low blood pressure and, according to Collier, is incompatible with a high blood pressure; but symptoms described as neurasthenia occur in association with a raised blood pressure and may be of a different significance, presumably due to the same toxic or other cause responsible for the hyperpiesis.

ENDOCRINE DISORDERS

Exophthalmic Goitre. Divergent opinions have been expressed as to the state of the blood pressure; in the early stage it has been stated that it is low by some, or high by others, and vice versa in the later stages, and no doubt there are variations due to various factors. But it now seems to be fairly well established that in well-marked cases the systolic pressure is raised more than the diastolic and that the differential or pulse pressure is therefore increased. My own experience is that the systolic pressure is usually raised to about 160 mm. Hg, as the result of the nervous condition, and that this distinguishes it from ordinary goitre. In hypothyroidism and myxœdema the blood pressure, contrary to what might be expected, may be normal.

The association of a toxic adenoma of the thyroid with a cortical adrenal tumour is interesting, for it has been thought that the adrenal cortex normally controls the activity of the thyroid, and on these grounds extract of adrenal cortex has been given in exophthalmic goitre (Shapiro and Marine). Though this form of treatment has not entirely escaped criticism (Achard), it has not attracted much attention. A few cases of the combined lesions with high blood pressure, as if the normal control exerted by the adrenal cortex had been lost, have been recorded (Keyser and Walters).

In connection with cases resembling exophthalmic goitre, but

with little or no palpable enlargement, it is interesting to note that Shapiro has taken quite a different view of their nature and describes them as a definite syndrome under the title "clinical symptomatic hyperepinephrinism." The signs of this syndrome, of which he and Boas have now published eight examples, are increased basal metabolic rate (hyperthermia), high systolic blood pressures, rapid pulse, loss of weight, nervousness, and pigmentation. These signs are common to exophthalmic goitre, but in the new condition there was absence of sweating, of the fine tremor, well marked asthenia, gastro-intestinal crises, thyroid enlargement, of improvement under iodine or X-ray treatment, and in three cases after subtotal thyroidectomy; another difference is that whereas the prognosis in Graves' disease is usually good both as regards control of symptoms and life, the outlook in the new syndrome is bad, three out of the eight patients having already died. The obvious criticism, already made by Read, that these are cases of Graves' disease with merely a coincident high blood pressure is met by the following objections that, in addition to other differences mentioned above, in Graves' disease the diastolic pressure is normal or low giving rise to a large pulse-pressure, which Davies and Eason have shown to be correlated with hyperthyroidism and a raised metabolic rate, whereas in symptomatic hyperepinephrinism both diastolic and systolic pressures are high. For more than thirty years the possibility of a disease due to excessive or aberrant secretion by the medulla of the adrenals has been anticipated but not established; Shapiro does not mention any postmortem investigation of his three fatal cases, so presumably they were not obtained, but from the clinical point of view the occurrence of cases resembling Graves' disease but without goitre and with a high diastolic and systolic pressure deserves further investigation.

Reference may perhaps be made here to spontaneous gangrene which, like Raynaud's disease, has been ascribed by von Oppel of Leningrad to excessive secretion of adrenalin by the adrenals; in 1921 he argued that excess of adrenalin, which Sicard in 1927 ascribed to stimulation of the adrenal medulla by the testicular hormone, produced spasm and secondary nutritional disturbance of the vessel walls consisting in endothelial desquamation and muscular degeneration so that thrombosis occurred (suprarenal arteriosis,

gangræna arteritis suprarenalis). He lays stress on the difference of the blood pressure in the proximal and distal segments of the limbs being much greater in this condition than normal. As a remedy he performed excision of the left adrenal, and by 1927 had with his colleagues done this in 115 cases; Herzberg in 1926 collected 110 cases of suprarenalectomy, fifty-eight by von Oppel and other Russian surgeons; Leriche of Strassburg has performed the operation in six cases. But Sénèque, modifying Herzberg's collection, finds that out of 112 such operations there were fourteen cures and that time—the inexorable judge—appears to show that the operation has gone out of favor, for whereas in 1923 the number of reported operations was forty-four, it fell to fourteen in 1924, and one in 1925, and one in 1926.

The relations between a high blood pressure and primary tumours (hypernephromas) of the adrenals are of some interest. Hyperplasia and small adenomas of the cortex are common in arteriosclerosis and high blood pressure. In some cases of cortical hypernephroma producing the characteristic change in the secondary sexual characters (virilism in females), hirsuties and obesity, the systolic blood pressure has been high; Oppenheimer and Fishberg tabulate eleven cases of this kind in which there was reason to believe that the blood pressure was unduly raised. The hyperplasia and minute adenomas associated with arteriosclerosis, high blood pressure, and chronic nephritis, cannot reasonably be regarded as the cause of the hypertension; they might be regarded as due to deposits of cholesterol resulting from arteriosclerosis, or due to a metabolic disorder associated with that responsible for the high blood pressure. It is difficult to explain the high blood pressure sometimes associated with large cortical hypernephromas; my impression is that it is by no means constant, for it does not appear logical to refer it to the hypernephromatous tumour.

In a few cases of tumours of the medulla of the adrenal the blood pressure has been high; this naturally suggested that there has been an excessive secretion of adrenalin. On a priori grounds it would seem probable that innocent paragangliomas or pleochromocytomas of the adrenal medulla would be more likely than rapidly growing neuroblastomas or sympathicoblastomas (which are composed of primitive undifferentiated cells) or to ganglioneuromas (composed of appar-

ently mature ganglion cells) to produce a highly differentiated substance such as adrenal. Oberling and Jung found chromaffine masses in their case of paraganglioma, the size of a kidney, and speak of this as their usual structure among the rare examples (less than ten) on record. Cases of adrenal paragangliomas with paroxysmal high blood pressure have been recorded (Labbé, Tinel and Doumer; Oberling and Jung); Bergstrand published the case of an adrenal medullary paraganglioma in association with otherwise unexplained hypertrophy of the left ventricle, which is circumstantial evidence of high blood pressure. Labbé, Tinel, and Doumer make a point of the characteristic paroxysmal character of the high pressure, and Oberling and Jung, who confirmed this, explain the sudden variations, for example from $\frac{180}{150}$ to $\frac{220}{155}$ as due to disordered function of an adrenalin-producing tumour, and contrast it with the permanent high pressure in hyperpiesia. It appears, however, that paroxysmal attacks of high blood pressure may be associated with tumours of other parts of the body, such as œsophageal carcinoma (Harvier and Bariéty) and mediastinal lymphosarcoma (Villaret, Block, Bariéty and Lappas), and to other factors, so that they are not peculiar to neoplasms of the adrenal medulla.

In Addison's disease a low systolic pressure, even to 50 mm. Hg, is essential for diagnosis; I have seen it 65 mm. but not lower.

REFERENCES

ACHARD, C.: Clinique médicale de l'hôpital Beaujon, 1923, p. 418.

ADDIS, T.: *Arch. Int. Med.*, Chicago, 1922, vol. xxix, p. 539.

ALLBUTT, C.: "Arteriosclerosis: A Summary View," p. 47, 1925.

IDEM.: "Diseases of the Arteries Including Angina Pectoris," 1915, vol. ii, p. 333.

IDEM.: *Ibid.*, 1915, vol. i, p. 266.

ALVAREZ, W. C.: *Arch. Int. Med.*, Chicago, 1923, vol. xxxii, p. 17.

IDEM.: *Trans. Assoc. Am. Phys.*, Phila., 1924, vol. xxxix, p. 323.

ALVAREZ, W. C., MCCALLA, R. L., and ZIMMERMANN, A.: *Arch. Int. Med.*, Chicago, 1926, vol. xxxviii, p. 158.

ALVAREZ, W. C., and ZIMMERMANN, A.: *Arch. Int. Med.*, Chicago, 1926, vol. xxxvii, p. 597.

ANDREWES, F. W.: *St. Barth. Hosp. Rep.*, 1912, vol. xlviii, p. 9.

BARACH, J. H.: *Arch. Int. Med.*, Chicago, 1925, vol. xxxv, p. 152.

BERGSTRAND, H.: *Hygiea*, Stockholm, 1920, vol. lxxxii, p. 3321.

BOAS, E. P., and SHAPIRO, S.: *Journ. Am. Med. Assoc.*, Chicago, 1925, vol. lxxxiv, p. 1558.

IDEM.: *Am. Heart Journ.*, 1926, vol. i, p. 643.

BORDLEY, J., and BAKER, B. M.: *Bull. Johns Hopkins Hosp.*, Balt., 1926, vol. xxxvi, p. 320.
BRANCH, A., and LINDER, G. C.: *Journ. Clin. Investig.*, 1926, vol. iii, p. 299.
BRIGHT, R.: *Guy's Hosp. Rep.*, 1836, vol. i, p. 338.
BRUNTON, T. L.: *Lancet*, 1867, vol. ii, p. 97.
CASHMAN, Z.: *Am. Journ. Med. Sc.*, Phila., 1917, vol. cliv, p. 476.
CHRISTIAN, H. A.: The Oxford Medicine (Christian and Mackenzie), vol. iii, p. 641.
COWAN, J., and FLEMING, G. B.: *Quart. Journ. Med.*, Oxford, 1911-12. vol. v, p. 309.
CUSHING, H.: *Bull. Johns Hopkins Hosp.*, Balt., 1901, vol. xii, p. 290; and *Am. Journ. Med. Sc.*, Phila., 1902, vol. cxxiv, p. 375.
IDEM.: *Ibid.*, 1903, vol. cxxv, p. 1017.
IDEM.: *Boston Med. and Surg. Journ.*, 1903 vol. cxlviii, p. 250.
CUSHNY, A. R.: "Digitalis and its Allies," p. 212, 1925.
CUTLER, O. I.: *Arch. Path.*, 1928, vol. v, p. 365.
CYRIAI, E. F.: *Quart. Journ. Med.*, Oxford, 1919-20, vol. xiii, p. 148.
CYRIAX, R. J.: *Brit. Med. Journ.*, 1918, vol. ii, p. 572.
DALLY, J. F. H.: "High Blood Pressure," p. 160, 1926.
DAVIES, H. W., and EASON, J.: *Quart. Journ. Med.*, Oxford, 1924-25, vol. xviii, p. 36.
DAWSON, LORD: *Brit. Med. Journ.*, 1925, vol. ii, p. 1161.
DAWSON, B., HUME, W. E., and BEDSON, S. P.: *Brit. Med. Journ.*, 1917, vol. ii, p. 345.
DIXON, W. E., and HALLIBURTON, W. D.: *Journ. Physiol.*, Camb., 1914, vol. xlviii, p. 317.
DRAPER, G.: "Human Constitutions," Phila., 1924.
DUMAS, A.: *Journ. de méd. de Lyon*, 1923, vol. iv, p. 573.
DUMAS, A., et DUBOULOZ: *Lyon méd.*, 1927, vol. cxl, p. 589.
EVANS, G.: *St. Barth. Hosp. Rep.*, 1920, vol. liii, p. 21.
IDEM.: *Brit. Med. Journ.*, 1923, vol. i, p. 549.
FAIRLEY, N. A., and STEWART, C. A.: "Cerebrospinal Fever," Commonwealth of Australia Service Publication, No. 9, Melbourne, 1916.
FISHBERG, M. H.: *Am. Journ. Med. Sc.*, Phila., 1927, vol. clxxiii, p. 835.
FISHER, J. W.: *Journ. Am. Med. Assoc.*, Chicago, 1914, vol. lxiii, p. 1752.
FOSSIER, A. E.: *Am. Journ. Med. Sc.*, Phila., 1926, vol. clxxi, p. 496.
FOX, F.: *Proc. Roy. Soc. Med.*, 1927, vol. xx (Gener. Rep.), p. 13.
FRIEDLANDER, A.: "Hypotension" Medical Monographs, vol. xv, 1927, Cincinnati.
GALLAVARDIN: "La tension artérielle en clinique," 1920.
GIBSON, G. A.: *Edin. Med. Journ.*, 1908, vol. xxiii, p. 17.
GIBSON, P. C.: *Lancet*, 1927, vol. ii, p. 1012.
GOODHART, J.: *Practitioner*, 1898, vol. lxi, p. 11
HALES, S.: "Haemastatics," 1733, vol. ii, p. 3.
HARE, H. A.: *Therap. Gaz.*, 1910, 3 ser., vol. xxvi, p. 457.
HARVIER, P., ET BARIÉTY, M.: *Bull. et mém. Soc. méd. des. Hôp. de Paris*, 1925, 3.s., vol. xlix, p. 176.
HEITZ, J.: *Paris méd.*, 1917, vol. xxiii, p. 112.
HERZBERG: *Arch. f. klin. Chir.*, 1926, vol. cxliii, p. 125.
HILL, L., and BARNARD, H. L.: *Brit. Med. Journ.*, 1897, vol. ii, p. 904.

HILL, L., FLACK, M., and HOLTZMANN, W.: *Heart*, London, 1909–10, vol. i, p. 73.
HILL, L., and ROWLANDS, R. A.: *Ibid.*, 1911–12, vol. iii, p. 219.
HURST, A. F.: "The Constitutional Factor in Disease," Psyche Miniatures, Medical Series, p. 58, 1927; and *Brit. Med. Journ.*, 1927, vol. i, p. 866.
JANEWAY, T. C.: "Clinical Study of Blood-Pressure," 1904, N. Y.
IDEM.: *Arch. Int. Med.*, Chicago, 1913, vol. xii, p. 755.
IDEM.: *Bull. Johns Hopkins Hosp.*, Balt., 1915, vol. xxvi, p. 341.
KAUFMANN, J., and CASHIN, M. F.: *Journ. Canad. Med. Assoc.*, Montreal, 1924, vol. xv, p. 37.
KEITH, N. M., WAGENER, H. P., and KERNOHAN, J. W.: *Arch. Int. Med.*, Chicago, 1928, vol. xli, p. 141.
KEYSER, L. D., and WALTERS, W.: *Journ. Am. Med. Assoc.*, Chicago, 1924, vol. lxxxii, p. 87.
LABBÉ, M., TINEL, J., et DOUMER: *Bull. et mém. Soc. méd. des hôp. de Paris*, 1922, 3 s., vol. xlvi, p. 982.
LANE, W. A.: "Operative Treatment of Intestinal Stasis," p. 119, 1918.
LERICHE, R.: *Bull. et mém. Soc. nat. de chir.*, 1926, vol. lii, p. 521.
MCCRAE, T.: In "Osler's Principles and Practice of Medicine," p. 864, 10th Edition, 1925.
MACKENZIE, J.: *Heart*, London, 1910–11, vol. ii, p. 284.
IDEM.: *Brit. Med. Journ.*, 1918, vol. i, p. 101.
IDEM.: "Angina Pectoris," p. 105, 1923.
IDEM.: "Diseases of the Heart," 3rd Edition, p. 100.
MACWILLIAM, J. A.: *Physiological Reviews*, Balt., 1925, vol. v, p. 303.
MAJOR, R. H.: *Journ. Am. Med. Assoc.*, Chicago, 1926, vol. lxxxvii, p. 311.
MAJOR, R. H., STOLAND, O., and BUIKSTRA, C. R.: *Bull. Johns Hopkins Hosp.*, Balt., 1926, vol. xxxix, p. 112.
MAREY: "Travaux du Laboratoire," Paris, 1875.
MARFAN, A. B.: *Compt. rend. Soc. biol.*, Paris, 1891, 9e. sér., vol. iii, p. 346; and *Rev. de méd.*, Paris, 1907, vol. xxvii, p. 1005.
MARTIN, C. J.: *Brit. Med. Journ.*, 1905, vol. i, p. 865.
MEAKENS, J.: "Arterial Hypertension and Hypotension and Their Clinical Significance," *Physiological Reviews, Balt.*, 1927, vol. vii, pp. 431–497.
MICHELL, R. W.: "System of Medicine" (Allbutt and Rolleston), 1909, vol. vi., p. 201.
MOOTS, C. W.: *Brit. Med. Journ.*, 1926, vol. ii, p. 295.
MOSCHCOWITZ, E.: *Arch. Int. Med., Chicago*, 1924, vol. xxxiii, p. 566.
IDEM: *Jour. Am. Med. Assoc.*, Chicago, 1928, vol. xc, p. 1526.
MURRAY, J. R.: *Brit. Med. Journ.*, 1914, vol. i, p. 697.
NAUCLER, R.: *Acta Med. Scandinav.*, 1919, vol. lii, p. 271.
NEWBURGH and MINOT: *Arch. Int. Med.*, Chicago, 1914, vol. xiv, p. 48.
NOLF, P., et FIRKET, J.: *Arch. méd. belg.*, 1918, vol. lxxi, p. 380.
NORRIS, BAZETT, and MCMILLAN: "Blood Pressure: Its Clinical Applications," 1928.
OBERLING, C., et JUNG, G.: *Bull. et mém. Soc. méd. des hôp. de Paris*, 1927, 3 s., vol. li, p. 366.
O'HARE, J. P., and WALKER, W. G.: *Arch. Int. Med.*, Chicago, 1924, vol. xxxiii, p. 343.

O'HARE, J. P., WALKER, W. G., and VICKERS, M. C.: *Trans. Assoc. Am. Phys.*, Phila., 1924, vol. xxxix, p. 320.
OPPENHEIMER, B. S., and FISHBERG, A. M.: *Arch. Int. Med.*, Chicago, 1924, vol. xxxiv, p. 631.
PHIPPS, C.: *Boston Med. and Surg. Journ.*, 1915, vol. clxxiii, p. 476.
PINES, N.: *Brit. Journ. Ophthalmol.*, London, 1927, vol. xi, p. 489.
POISEUILLE, J. L. M.: "Recherches sur la force du coeur aortique," *Journ. de physiol.*, Paris, 1828, vol. viii, p. 272.
POTAIN: "La pression artérielle de l'homme," 1902.
PRICE, F. W.: *Brit. Med. Journ.*, 1912, vol. ii, p. 689.
READ, J. M.: *Am. Journ. Med. Sc.*, Phila., 1926, vol. clxxi, p. 227.
REID, C.: *Quart. Journ. Med.*, Oxford, 1925-26, vol. xix, p. 411.
RIVA-ROCCI: *Gazz. med. di Torino*, 1896, vol. xvlii, p. 981.
ROBINSON, G. C.: *Arch. Int. Med.*, Chicago, 1910, vol. v, p. 482.
ROLLESTON, H.: *Heart*, London, 1912–13, vol. iv, p. 83.
RYLE, J. A.: *Guy's Hosp. Rep.*, 1927 (Bright Centenary No.), vol. lxxvii, p. 307.
SAHLI: *Verhandl. Congr. f. inn. Med.*, 1901, vol. xix, p. 45.
SÉNÈQUE, J.: *Presse méd.*, Paris, 1927, vol. xxxv (i), p. 451.
SEWELL, H.: *Am. Journ. Med. Sc.*, Phila., 1919, vol. clviii, p. 786.
SHALET, L.: *New York State Journ. Med.*, 1914, vol. xiv, p. 189.
SHAPIRO, S.: *Endocrinology*, Los Angeles, 1926, vol. x, p. 413.
SHAPIRO, S., and MARINE, D.: *Ibid.*, 1921, vol. v, p. 599.
SHAW, H. B.: "Hyperpiesia and Hyperpiesis," p. 171, 1922.
SICARD: *Bull. et mém. Soc. méd. des hôp. de Paris*, 1927, 3e s., vol. li, p. 443.
SOPHIAN: "Epidemic Cerebrospinal Meningitis," 1913.
STARLING, E. H., and ANREP, G. V.: *Proc. Roy. Soc.*, 1925, vol. xcvii, B., p. 463.
STARLING, H. J.: *Lancet*, 1906, vol. ii, p. 846.
STIVELMAN, B. P.: *Am. Journ. Med. Sc.*, Phila., 1927, vol. clxxiii, p. 46.
STOCKS, P., and KARN, M. N.: "Blood-Pressure in Early Life," Drapers' Company Research Memoirs, Camb., 1924, vol. i.
SYMMERS, D.: *Am. Journ. Dis. Child.*, Chicago, 1917, vol. xiv, p. 463.
SYMONDS, B.: *Journ. Am. Med. Assoc.*, Chicago, 1923, vol. lxxx, p. 232.
TZANCK, A., et RENAULT, P.: *Bull. et mém. Soc. méd. des hôp. de Paris*, 1927, 3e. s., vol. li, p. 1441.
VAN LEERSUM, E. C.: "Old Physiological Experiments," *Janus*, Leyde, 1913, vol. xviii, p. 325.
VASCHIDE, N., et LAHY, J. M.: *Arch. gén. de méd.*, Paris, 1902, vol. cxc, pp. 349, 480, 602, 711.
VILLARET, BLOCK, BARIÉTY, et LAPPAS: *Presse méd.*, Paris, 1926, vol. xxxiv, p. 856.
VON OPPEL, W. O.: *Lancet, London*, 1922, vol. ii, p. 116.
IDEM.: *Lyon chir.*, 1927, vol. xxiv, p. 1.
VON RECKLINGHAUSEN: *Arch. f. exper. Path. u. Pharm.*, 1901, vol. xlvi, p. 110.
WEISS: *Ztschr. f. klin. Med.*, 1923, vol. xcvi, p. 151.
WHITE, P. D., and MUDD, S. G.: *Trans. Assoc. Am. Phys.*, Phila., 1927, vol. xlii, p. 263.
WILLIAMSON, O. K.: *Brit. Med. Journ.*, 1921, vol. i, p. 734.
WINDLE, J. D.: *Quart. Journ. Med.*, Oxford, 1916–17, vol. x, p. 274.
WOLFERTH, C. R.: *Am. Journ. Med. Sc.*, Phila., 1927, vol. clxxiv, p. 760.
WORSTER-DROUGHT, C., and KENNEDY, J. M.: "Cerebrospinal Fever," pp. 275–288.